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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/498,135	02/04/2000	John F. Stone	36435.0100	8366

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	22

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/498,135	STONE, JOHN F.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-13 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10-13 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 8, 2002 has been entered.

2. This action is in response to the papers filed July 8, 2002. Currently, claims 1-7, 10-13, 15-17 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-7, 10-13, 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherry et al. (Mutation Research, Vol. 275, pg. 57-67, 1992) or Chen et al (Mutation Research, Vol. 256, pg. 21-27, 1991) or Parshad et al (PNAS, Vol. 93,

pg. 5146-5150, May 1996) in view of Marcon (Mutation Research, Vol. 445, pg 155-166) and further in view of Gorczyca et al (Cancer Research, Vol. 53, pg. 1945-1951, April 1993) or Yager (US Pat. 5,932,418, August 1999).

Cherry et al. (herein referred to as Cherry) teaches facilitating disease diagnosis by exposing cells of a suspected diseased patient to a chromosome damaging agent which induce chromosome breakage and broken ends, marking some of the chromosome fragments, and analyzing the fragments to determine whether cells were affected by the disease. Specifically, peripheral blood lymphocytes from patients with Alzheimer's disease (AD) and controls were grown in culture for 72 hours with phytohemagglutinin (mitogen)(pg. 60, col. 2)(limitations of Claims 1a, 2 and 3). Then the cells were treated with bleomycin, which causes an activated oxygen radical, or with methyl methane sulfonate (MMS) (chromosome damaging agents)(abstract)(limitations of Claim 1a, 6-7, 13, 15). Then cells were harvested, fixed on slides, and marked with Giemsa stain (limitations of Claim 4). 50 cells/ patient were scored for chromosome damage. Cherry teaches that bleomycin will induce DNA strand brakage at any point during the cell cycle (page 60, col. 2). Comparison between patients with Alzheimer's and control patients was performed to determine whether a significant difference existed (limitations of Claims 14, 16 and 17). As seen in Figure 1, bar charts are presented which show significant differences between AD women and control women with bleomycin (pg. 62). Cherry teaches that when considering women, bleomycin is a very effective marker for AD (pg. 65, col. 1).

Chen et al. (herein referred to as Chen) teaches facilitating disease diagnosis by exposing cells of a suspected diseased patient to a chromosome damaging agent, marking some of the chromosome fragments, and analyzing the fragments to determine whether cells were affected by the disease. Specifically, Chen teaches a sampling cells and transforming by Epstein-Barr virus to establish lymphoblastoid cell lines (pg. 22, col. 1). Cells were cultured in agar and subjected to irradiation (a chromosome damaging agent)(pg. 22, col. 2)(limitations of Claim 2). The colonies with 50 or more cells were isolated to determine the frequency of radiation-inducted aberrations. The cells were fixed, spread on slide, and stained with Giemsa to mark the chromosomes (pg. 22, col. 2)(limitations of Claim 4). Upon studying of the cells, a higher frequency of chromosome-type lesions was observed in AD cells, indicating the cells from AD patients were more radiosensitive than normal patients (pg. 25, col. 1). 12 or 14 patients show sensitivities greater than cells from age-matched controls (pg. 26, col. 1). Chen's analysis finds that AD cells are hypersensitive to gamma-radiation, based on induced chromosomal aberrations (page 26, col 1).

Parshad et al. (herein referred to as Parshad) teaches a method for facilitating disease diagnosis by exposing cells of a suspected diseased patient to a chromosome damaging agent, marking some of the chromosome fragments, and analyzing the fragments to determine whether cells were affected by the disease. Specifically, Parshad teaches sampling skin fibroblasts and blood from patients diagnosed with Alzheimer's and control patients. The heparinized blood was mixed with phytohemagglutini (mitogen) and incubated for 48 or 68 hours (limitations of Claims 2

and 3). The lymphocyte cultures were subjected to either fluorescent light or 254 nm UV light (chromosome damaging agent that causes free radical-induced DNA damage) (pg. 5147, col. 1, para. 3 and 4)(limitations of Claim 6). Moreover, the cells were then treated with beta-cytosine arabinoside (araC) or caffeine (repair retarding agents) (limitations of Claim 5 and 12). Chromatid breaks were quantitated using cytogenetic analysis of metaphase cells.

Neither Cherry, Chen nor Prashad not explicitly teaches a method of diagnosing Alzheimer's using interphase cells and marking of the chromsome fragments using dNTP and fluoresceinated material.

However, Marcon et al. (herein referred to as Marcon) teaches a method of detecting chromosome damage and aneuploidy detected by interphase multicolour FISH in benzene-exposed shale oil workers. Marcon teaches the simultaneous detection of both chromosome breakage, involving damage-prone pericentromeric regions and hyperploidy in interphase cells (abstract). Marcon teaches that cultured lymphocytes of the benzene-exposed workers compared to the unexposed controls were modestly increased frequencies of breakage, suggesting an expression of premutagenic lesions during the S-phase in vitro (abstract). Myeloid leukemia-inducing agents include benzene (pg 164, col. 1). Macron also teaches that tandem labelling FISH can be usefully applied to human biomonitoring at interphase in different cell types (abstract). Macron teaches that the methodology was applied to interphase blood smear cells and culture lymphocytes, demonstrating the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2). The

lymphocyte cultures were established, harvested 48 hours following mitogen stimulation (abstract)(limitations of Claim 2, 3). Marcon teaches that "one advantage to the application of tandem labelling is the ability to detect chromosome changes in interphase nuclei, in addition to metaphase cells. As a result different cell types including those not amenable for metaphase analysis, can be investigated" (pg 163, col. 2). Further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1).

Moreover, Gorczyca et al. (herein referred to as Gorczyca) teaches a method of detecting DNA strand breaks by in situ terminal deoxynucleotidyl transferase and nick translation. Gorczyca teaches sampling peripheral blood cells and culturing the cells (pg. 1945-1946)(limitations of Claim 2). After treatment the cells were subjected to in situ assays including the NT and TdT assay. For the NT assay, the cells were suspended with nick translation buffer, dATp, dGtp and dCTP and biotin-16-dUTP (pg. 1946, col. 1), the incubated with fluoresceinated avidin (limitations of Claim 1 b). For the TdT assay, fixed cells were suspended in a solution containing biotin-16-dUTP and dATP, dGTP and dCTP, this incubated with fluorescented avidin (limitations of Claims 1 b). Gorczyca teaches that the advantages of TdT or NT assays include the direct labeling of 3'-OH termini of the DNA breaks (pg. 1950, col. 2)(Limitation of Claim 6). Further, image analysis or flow cytometry was performed to detect fluorescence emissions from each cell and the data was stored and analyzed (pg. 1946, col. 1)(limitations of Claim 10). Gorczyca illustrate numerous means by which chromosome breaks may be analyzed. Gorczyca specifically states that the response of human

leukemias to various drugs can be monitored with the TdT assay, implying that Gorczyca is indirectly diagnosis of disease state. The terminal deoxynucleotidyl transferase (Tdt) method is specific toward the detection of 3'OH termini in DNA strand breaks.

Yager teaches a sensitive bioassay which is used in testing for genotoxic agents. Yager teaches staining for fragmentation of DNA associated with genotoxic damage. Yager teaches the TUNEL assay is used to detect 3'OH termini of nicked or broken DNA strands. The nicks or breaks may be generated directely by a genotoxic agent or indirectly through triggering of apoptosis (col. 14, lines 8-15).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the chromosome breakage detection methods of Cherry, Chen or Prashad to predict the AD state of individuals with the method of Marcon for determining chromosome damage in interphase cells and further using a method of adding dNTP and detecting the chromosome breaks, as taught by Gorczyca or Yager. The ordinary artisan would have been motivated to have analyzed interphase cells using the method of Marcon, rather than the metaphase cells of Cherry, Chen or Prashad, for the expected benefits of the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2) including those different cell types including those not amenable for metaphase analysis, and further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1). The ordinary artisan would have realized that expanding the method of Cherry, Chen and

Prashad to include studying interphase cells as taught by Marcon would vastly increase the information gained with respect to the chromosome breakage in a cell. Therefore, analyzing interphase cells would add increased benefits over metephase cells. Moreover, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cherry, Chen, or Prashad in view of Marcon to include the labeling of the chromosomal fragments with biotin-16-dUTP and exposing to fluoresceinated avidin as taught by Gorczyca or Yager. Yager teaches that the TUNEL assay is used to detect 3'OH termini of nicked or broken DNA strands which may have been generated directely by a genotoxic agent or indirectly through triggering of apoptosis. The ordinary artisan would be motivated to have performed the method of Cherry, Chen or Prashad in view of Marcon and labeled the fragments with biotin and fluoresceinated in order to allow rapid detection with flow cytometry and amenable to automation as taught by Gorczyca. The art clearly teaches that the terminal deoxynucleotide transferase assay or TUNEL method can be used to detect DNA fragmentation or chromosome breaks. The terminal deoxynucleotidyl transferase (Tdt) method is specific toward the detection of 3'OH termini in DNA strand breaks. The method has the benefit of sensitivity, direct labeling of 3'-hydroxyl termini of DNA breaks such that the breaks are identifiable at the molecular level and early detection. Therefore, the ordinary artisan would have been motivated to have detected chromosome breaks which contain a 3'OH termini on the DNA strand using a known method which is sensitive to the 3'OH termini detection, such as terminal deoxynucleotidyl transferase (TdT).

Response to Arguments

The response traverses the rejection. It is noted that each of the limitations of previous Claim 8-9 has been added to independent Claim 1. The response asserts that Claims 8-9 have been cancelled and therefore, the rejection is moot. While Claims 8-9 have been cancelled, Claims 8-9 have been incorporated into Claim 1. Therefore, the rejection is not moot. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

4. No claims allowable over the art.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
August 9, 2002

W. Gary Jones
Supervisory Patent Examiner
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